Ph.D. SYNOPSIS

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CATEGORY	**SC**
SUBJECT	Pharmaceutical Science
Ph.D. SYNOPSIS TITLE	**"** Pharmacognostic and Pharmacological Evaluation of Medicinal Plant Formulations for Anti-thyroid Activity**"**
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DATE OF R.A.C.	29/04/2019
DATE OF R.R.C.	22/07/2019
PLACE OF R.R.C.	**S.R.T.M University, Nanded.**

Pharmacognostic and Pharmacological Evaluation of Medicinal Plant Formulations for Anti-thyroid Activity

A SYNOPSIS SUBMITTED FOR THE REGISTRATION OF *DEGREE OF*

DOCTOR OF PHILOSOPHY

“ Pharmacognostic and Pharmacological Evaluation of Medicinal Plant Formulations for Anti-thyroid Activity**”**

In the Faculty of Pharmaceutical Sciences & Technology

Submitted

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(2019)

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- **Abstract of proposed work plan/ problem:**

Thyroid gland regulates a wide range of physiological activates such as growth, metabolism, homeostasis and cell proliferation and differentiation. Hyperthyroidism has several causes. Graves disease is the most common cause, is an autoimmune disorder associated with the development of long acting thyroid stimulating antibodies (LATS). Single or multiple thyroid nodules that produce thyroid hormone can also cause hyperthyroidism. The use of excessive dosed of thyroid hormone supplement levothyroxine, is also common cause.

Consequence of untreated hyperthyroidism includes arterial fibrillation, congestive heart failure, osteoporosis and neuropsychiatric disorders. Hyperthyroidism causes symptoms that reduce functional status and quality status of life.

Medicinal plants have been identified and used by humans through history. To name the herbs a natural antioxidants used to treat thyroid disorders including hyperthyroidism and hypothyroidism. Herbal drugs have comparatively fewer side effects. It is believed that the drugs derived from plants very safe and produce significant effects in the treatment of various diseases. Today traditional medicines are being widely used and plants are still considered a major source of natural antioxidants that can serves as clue for the development for new drugs.

Keywords- Hyperthyroidism, Medicinal plants and Pharmacological screening

2. Introduction:

Hyperthyroidism (having too much thyroid hormone). The condition is also called as thyrotoxicosis (overproduction of thyroid gland). Normally hypothalamus is located at the base of the brain. Detect low blood level thyroid of hormone. Release of thyrotrophic releasing hormone. Anterior pituitary releases thyroid stimulating hormone (TSH) or thyrotropin. TSH stimulates the thyroid gland which is located in the neck. The thyroid gland is made up of thousands of follicles which is small sphere which lined with follicular cells .follicular cells converts thyroid globules in a portion found in follicle into two iodine containing hormone .tri-iodothynin (T_3) and Thyroxin (T_4).Once these hormones releases from thyroid gland these hormones entered the blood and bind with the circulating plasma proteins only small amounts T_3 and T_4 are travelled unbound to the plasma proteins and these two hormone gets effectors in every cell in the body once it enter into cell T_4 is mostly converted into T_3 while it exert into fat e.g., the cell may produce more protein to burn up the more energy from carbohydrates or fat. T_3 increases cardiac output, stimulates bone reabsorption activates sympathetic nervous system. The part of nervous system involved the flight and fight response [3,5].

Causes:

All results in too much thyroid hormone and a hyper metabolic state.

The most common cause is a Graves disease. It is an autoimmune disease β- cells produce antibodies against thyroid patients –thyroid stimulating immunoglobulin's which bind to the TSH receptor on a follicular cells and immediate TSH. This results in growth of thyroid gland and to stimulate the follicular cells to produce excess thyroid hormone.

Another main cause is toxic nodular goitre- follicles starts generating lots off thyroid hormone. In some cases mutated TSH receptor improperly keeps follicular cells active.

Hyper functioning of thyroid adenoma- Where follicular cells uncontrollably forming benign tumour making excess thyroid hormone.

Any time thyroid gets damaged / inflamed because large release of free forms of thyroid hormone.

Jod – Basedow syndrome (Iodine induced thyrotoxicosis). Develops after Iodine deficient person gets heavy dose of Iodine.

Neonatal hyperthyroidism – Newborns / mothers who have Graves disease generating too much thyroid hormone in response to thyroid stimulating immunoglobulin's crosses the placenta and injuries to baby.

Sign and symptoms include:

Weight loss (despiteincreased appetite), increases basal metabolic rate. Heat intolerance-body producing more heat.An rapid hearts rates, sweating, hyperactivity, anxiety and insomnia because the effect of thyroid hormone on sympathetic nervous system.

Thyroid strom - life threatening complications where body gets to state of severe hyper metabolism, where someone stops treatment develops infection and has surgery.

Diagnosis:

1. Measuring blood level of TSH, T_3 and T_4

Primary cause – TSH will be low and unbound thyroid hormone will be high.

2. Radioactive Iodine uptake test and thyroid scan [3,5].

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3. Review of Literature and Development in the subject (Previous work done in the relevant area):

1. **Anshi Tiwari, And Ashish Manigauha, in their studies "Evaluate the Anti-Thyriod activity of Hydro alcoholic Extract of *Coriander sativum* in Experimental Animals" 2018; 9(1); 315 – 321:** In this study the hyperthyroidism was induced to albino rats orally using propyl thio-uracil (PTU) for 14days.The hyperthyroidism rats were administered Hydroalcoholic extract of *Coriander sativum* seeds (250mg/kg and 500mg/kg) for 21 days.The serum was analysed for thyroid hormone level. Results demonstrated that 250mg/kg and 500mg/kg of hydroalcoholic extracts produce significant anti-thyroid activity by decreasing theT_3 and T_4level and lowered the TSH level in rats. The histopathological study of the thyroid gland justifies the anti-thyroid activity of *Coriander sativum* seeds.The finding of this study propose that the extract may have property to regulate thyroid level in the animals
2. **MohommedAzharuddin, Mohammed Atif, Mohammed Ibrahim Ahemed, Syed Asadulla, Bakhtiary, Mohommed Ibrahim in their studies "Evaluation of Anti-thyroid Activity of *Ficusrecemosalinn* nark in male rats"2014; 7(3); 118-122:** In this study they revealed that *Ficusrecemosa* genus exhibited the presence of thyrosine which is responsible for the formation of T_3 and T_4 hormones.Hyperthyroidism was induced in experimental rats by administrating Thyroxine (600µ/kg/ml) orally for 14 days.Hyper thyroid male albino rats weighing 150-200g were treated with oral dosed of 250 mg/kg 350mg/kg and 450mg/kg of *Ficusrecemosa* ethanolic extracts for a period of 21days served as standard. In this study morphological assessment demonstrated that thyroxine treated gathering demonstrates increased lavel of Triiodo-L-thyonine and L- thyroxine. Simultenious administration of ethanolic extract of *Ficus recemosa* bark lowered the increased level.The decrease in the level of T_3 and T_4 by the extract was compared with the referencing drug Methimazole.
3. **Anshita Gupta, Suchita Wamankar, BinaGidwani, Chnachal deep kour, "Hrbal drugs for Thyroid Treatment" 2016; 6(1); 62-70; in** their studies revelead that the herbal drugs used for the treatement for hyperthyroidism. Herbal drugs have proven to be usefull in number of diseases. This study has releaved that the some herbal drugs shows the synergistically grat effect for the treatment of hyperthyroidism and

hypothyroidism.Some drugs study have been dione in this journal such as *Lycopus virginicus, Melissa Officinalis, Lenurus cardiac, Lithosepermumruderale, Rosmarinusofficinalis, Slivia officinalis, Centellaasiatica, Witheniasomnifera, Comiphoramukul, Plectranthusbarbatus, Fucusvesiculosus.* This plant shows the remarkably lowering the symptoms of hyperthyroidism and hypothyroidism.

4. **Arvind Kumar Shakya, 2016:4(4):59-64:** in their studies, they revealed the study about the traditional medicinal plants, medicinal play an important role in preventing and treating of human disease. People have been using plant as traditional medicine for thousands year ago.Plants have been associated with the development of human civilization around the whole world. However, plants are have a fewer side effect as compare to conventional drugs. Conventional drugs are available for hyperthyroidism disorder cure symptomatically. Herbal drugs have the capacity to cure such metabolic disease synergistically at different steps. In this study they summarisingto various plants for hyperthyroidism and related disorders effectively.
5. **Mridul Ranajan, Ramteke Rajkala and Thakar Anup; "Review on Ayurvedic Management of Hypothyroidism with Critical Analysis " 2015; 3(9); 83-88: in this study they revealed that** Hypothyroidism is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. The cardinal symptoms of hypothyroidism are weight gain, fatigue, cold intolerance, hoarseness of voice, selling of limbs and puffiness of face etc. Levothyroxine (synthetic S.T4) is the most effective hormone replacement for the treatment of hypothyroidism, Now a day physicians are adding lilothyronin (synthetic $S.T_3$) to provide better symptom control, but this has not been confirmed by studies. Ayurvedic management of hypothyroidism is much effective and preventive as compare to modern treatment. Purification followed by palliative therapy was found as a suitable treatment plan to manage hypothyroidism. All the Ayurvedic therapies adopted as a part of various research studies proved to have significant results in the management of hypo-thyroidism. Among the purification therapies, controlled induced emesis procedure was the most commonly adopted purificatory process with maximum efficacy. It also revealed the fact that all the therapies were found to be significantly effective and clinically safe as no adverse drug reaction were reported during treatment period among any of the screened studies.
6. **Norakant Neupane, Manpreet Kaur and Pranav Kumar Prabhakar "Treatment of Hashimoto's thyroiditis with herbal medication" 2017; 11(3), in this** review article

summarizes the herbal treatments which are commonly used and also their mechanism of action.Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder, an organ-specific disease, which is characterized by diffused goitre with lymphocytic infiltration, which leads to destruction of thyroid gland causing hypothyroidism. This is a condition where the thyroid gland does not release enough of thyroid hormone called thyroxin due to the insufficient amount of iodine. Some common sign and symptoms of Hashimoto's disease and hypothyroidism are weight gain, depression, and constipation, irregular and heavy menstrual period. However, herbal treatment is effective and enhances thyroid function. There are some natural-occurring herbs such as gum guggul (*Commiphora mukul*), Blue flag root (*Iris versicolor*), bladder wrack (*Fucus vesiculosus*), and seaweeds which are commonly used to treat this disorder. These herbs have different mechanism of action in HT and hypothyroidism disorder. Bladder wrack upregulate the production of iodine processing hormone, whereas gum guggul increases the conversion of tetraiodothyronine into triiodothyronine, and blue flag root is a detoxifying agent.

7. **Mara Ventura, Miguel Melo, and Francisco Carrilho "Selenium and Thyroid Disease: From Pathophysiology to Treatment" 2017: 2-9:** in their study he revealed that. Selenium is a micronutrient embedded in several proteins. In adults, the thyroid is the organ with the highest amount of selenium per gram of tissue. Selenium levels in the body depend on the characteristics of the population and its diet, geographic area, and soil composition. In the thyroid, selenium is required for the antioxidant function and for the metabolism of thyroid hormones. Methods. Regarding thyroid pathology, selenium intake has been particularly associated with autoimmune disorders. The literature suggests that selenium supplementation of patients with autoimmune thyroiditis is associated with a reduction in antithyroperoxidase antibody levels, improved thyroid ultrasound features, and improved quality of life. Selenium supplementation in Graves' orbitopathy is associated with an improvement of quality of life and eye involvement, as well as delayed progression of ocular disorders. The organic form of selenium seems to be the preferable formulation for supplementation or treatment. Conclusion. Maintaining a physiological concentration of selenium is a prerequisite to prevent thyroid disease and preserve overall health. Supplementation with the organic form is more effective, and patients with autoimmune thyroiditis seem to have benefits in immunological mechanisms. Selenium supplementation proved to be clinically beneficial in patients with mild to moderate Graves' orbitopathy.

8. **Ali Karimi1, Maedeh Majlesiand Mahmoud Rafieian-Kopaei1 "Herbal versus synthetic drugs; beliefs and facts" 2015; 4(1); 27-30; in this study they revealed about** Herbal therapy is a holistic therapy, integrating emotional, mental and spiritual levels. Life style, emotional, mental and spiritual considerations are part of any naturopathic approach. The use of herbs does not generally involve "drug" actions or adverse effects. Although medicinal plants are widely used and assumed to be safe, however, they can potentially be toxic. Where poisoning from medicinal plants has been reported, it usually has been due to misidentification of the plants in the form, in which they are sold, or incorrectly preparation and administration by inadequately trained personnel. There are some "drug like" plants remedies that their actions approach that of pharmaceuticals. Herbalists use these plants in treatment strategies and in countries such as Britain their vast availability is restricted by law. Digitalis is one of these examples and the number of these plants is not a lot. The mechanisms by which the herbs generally act are not established, however, most of medicinal plants possess antioxidant activities. The plants have been shown to effective by this property is various conditions including cancer, memory deficit and Alzheimer, atherosclerosis, diabetes and other cardiovascular diseases. Antioxidant activities of herbal medicines are also effective in reducing the toxicities of toxic agents or other drugs.

- **Objectives of Research/ Proposed Hypothesis:**

Need of Study:

Hyperthyroidism and hypothyroidism is a life threatening disorder which is caused due to improper functioning of thyroid gland. About 5 % of U.S adult report having thyroid disease or taking medication. In cross sectional study of 2,799 well functioning adults aged 70-79, 9.7 % of black women, 6 % of white woman, 3.2 % of black men and 2,.2 % of white women reported history of hyperthyroidism. Consequence of untreated hyperthyroidism includes arterial fibrillation, congestive heart failure, osteoporosis and neuropsychiatricdisorder. Both hyperthyroidism and hypothyroidism because symptoms that reduce functional status and quality of life.The present study evaluate the medicinal plants and natural products represents one of the most popular alternative treatment for the hyperthyroidism rather conventional drugs. Many of the natural products have hormonal activity and have long been used to prevent and treat diseases including thyroid and might be good. Whateverdevelopment ofthe synthetic drugs of ant thyroid.In the present study determined the anti-thyroid effects of various medicinal plants in the Maharashtra region exploit were found to be inhibiting uptake of thyroid hormone or radioactive iodine in manner similar to the antithyroidcompounds[3]**.**

Aim and objectives of Research Topics:

- To prepare various plant extracts and fractions for checking anti-thyroid potential and evaluated for preliminary phytochemical constituents.
- In-vitro Anti-oxidant activity of extract.
- Acute oral toxicity study of selected plant extracts.
- To prepare various formulation of plant extracts.
- To evaluate in-vivo pharmacological screening technique for anti-thyroid activity.

5. Methodology to be adopted:

On the basis of ethno medical information and literature survey, the plantmedicinal plants will selected for present study. The plan will divided into following section

1) Plant collection:

1) Collection, Identification and authentication of plant material.

The selected medicinal plants material will collected and will be authenticated by Taxonomist.

2. Processing of crude drug.

The selected medicinal plants material will subjected to shade drying and further crushed to powder and then the powder is passed through the mesh 14 and stored in air tight container for further use as per Indian Pharmacopeia.

3. **Pharmacognostic Evaluation**

1. Macroscopic features of plants material,
2. Microscopic features of plants material
3. Microscopical Evaluation of Powdered drug

4. Extraction of plant material- Selection of extraction method and extraction solvent will be selected on the basis literature survey, of the medicinal plants.

5. Phytochemical screening

1. Phytochemical screening plants material for carbohydrate, proteins, tannins, alkaloids, glycosides etc.determination.

2. Phytochemical qualitative analysis of extracts for TLC fingerprinting.

6. Pharmacological screening of plants material for acute oral toxicity and repeated dose toxicity.

1. Acute oral toxicity and repeated dose toxicity studies will be carried out for plant extract as per OECD guidelines

2. Pharmacological screening for antioxidant activity of plant extracts will be carried out.

3. Pharmacological screening for Anti-thyroid activity by suitable animal model by as per official standard reference.

7. Preparation of suitable dosage form.

8. Interpretation of data and its presentation.

6. Importance of study:

Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. India too, is no exception. According to a projection from various studies on thyroiddisease, it has been estimated that about 42 million people in. India suffers from thyroid diseases. Thyroid diseases are different from other diseases in terms of their ease of diagnosis, accessibility of medical treatment, and the relative visibility that even a small swelling of the thyroid offers to the treating physician. Early diagnosis and treatment remains the cornerstone of management.

The prevalence of hyperthyroidism has been studied in several studies. In an epidemiological study from Cochin subclinical and overt hyperthyroidism were present in1.6% and 1.3% of subjects participating in a community survey. In a hospital-based study of women from Pondicherry, subclinical and overt hyperthyroidism werepresent in 0.6% and 1.2% of subjects. More than a third of community-detected hyperthyroid cases have positiveanti-TPO antibodies, and about 39% of these subjects have goitre.

Population studies have suggested that about 16.7% of adultsubjects have anti-thyroid peroxidase (TPO) antibodies andabout 12.1% have anti-thyroglobulin (TG) antibodies.In this same study of 971 subjects, when subjects with abnormal thyroid function were excluded, the prevalenceof anti-TPO and anti-TG antibodies was 9.5% and 8.5%. In a landmark study of Hashimoto's thyroiditis inIndia, 6283 schoolgirls from all over the country werescreened. Among them, 1810 schoolgirls had a goitre. Among them 764 subjects underwent a fine needle aspiration cytology, and of these subjects, 58 (7.5%) had evidence ofjuvenile autoimmune thyroiditis (the term included both Hashimoto's thyroiditis and focal lymphocytic thyroiditis).Among fine needle aspiration cytology-confirmed cases of juvenile autoimmune thyroiditis, subclinical and over thypothyroidism were seen in 15% and 6.5%, respectively. (3)

Herbal drugs have proven to be useful in number of diseases. Metabolic disorders are some disorders which progress at a slower rate but damage the whole functioning of the body. Conventional drugs available for these disorders cure symptomatically. Herbal drugs have the capacity to cure such metabolic disorders synergistically at different steps.Today is the era of discovering new horizons in the field of medicines, specially through the exploration of phytoconstituents and secondary metabolites. A decade earlier the use of herbal drugs and phytomedicines was totally forgotten by the world because that was the time when alleopathic medicines were holding the monopoly of curing diseases and western science blindly rely on it. But in last few years herbal drugs have again proven their strong presence in treating various metabolic diseases like diabetes, hormonal imbalance etc.

►Significance of the study:

Research Outcomes:

1. The study will be supportive to treat various complications regarding the hyperthyroidism and their further complications.
2. Plant based medicinal expected to have fewer side effects as compare to modern drugs.
3. The present study will minimize the cost of treatment of disease to hyperthyroidism.
4. This study uses the plants as medicine which has been not fully explored that's why will bevery important investigate the anti- thyroid potential of these plants.
5. This study functional to isolate potent component of plants which have maximum anti-thyroid activity as compared to the synthetic drugs.

7. Proposed work Plan/ Formulation and Structure of Study:
Year-wise Plan of work and targets to be achieved:

Present study designed in such a way that it will comes to conclusive outcome within 03 years from the date of allocation. The year wise plan includes

YEAR 01

Literature survey, plant collection and authentication, preliminary screening, Macroscopic and microscopic evaluation, Drying Powdering, Physical evaluation of powdered drug will be carried out.

YEAR 02

Extraction of pant material will be carried out by suitable method of extraction, phytochemical evaluation of extracts / fraction by different qualitative and quantitative methods of evaluation (as per WHO guidelines). In – vitro Pharmacological screening of different extract for anti-oxidant activity.

YEAR 03

Preparation of suitable dosage form according to standard procedure and in-vivo screening for Anti-thyroid activity of different extract on suitable animal model. Pharmacokinetic and pharmacodynamic study of formulations will be carried out.

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1.	**Signature of Candidate**	
2.	**Remarks of the research Supervisor**	
3.	**Name & Designation of Guide** **Signature of research Supervisor**	
4.	**Signature of Director / Principal**	. **(Seal of The Institute)**